25. (Reiterated) The method of claim 1, wherein the individual is hypotensive.

26. (Amended) The method of any of claims 1 and 3-6, further comprising administering one or more of an anticoagulant, an antiplatelet agent, a thrombin inhibitor, and/or a thrombolytic agent.

27. (Amended) The method of any of claims 1 and 3-6, further comprising performing vascular surgery.

28. (Reiterated) The method of claim 27, wherein the vascular surgery comprises carotid endarterectomy.

31. (Amended) The method of any of claims 3-6 ~~claim 29~~, wherein treatment of the patient with the *hedgehog* polypeptide ~~*ptc* therapeutic~~ results in at least a 70% reduction in cerebral infarct volumes relative to absence of treatment with the *hedgehog* polypeptide ~~*ptc* therapeutic~~.

Please add the following new claim:

38. (New) The method of claim 1, wherein treatment of the individual with the *hedgehog* polypeptide results in at least a 70% reduction in cerebral infarct volume relative to absence of treatment with the *hedgehog* polypeptide.

add D7

REMARKS

Claims 1, 3-6, 18-23, 25-28, 31, and 38 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note the entry of the previously filed response, change of address, and change of attorney docket number, but respectfully point out that the Office Action was not mailed to the new address, nor was the docket number changed. Correction is respectfully requested.

2-10. Applicants note that claims 1-37 are pending and that the previous response has been considered. Applicants gratefully acknowledge that several rejections under 35 U.S.C. § 112, first and second paragraphs, and 35 U.S.C. §§ 102 and 103 have been withdrawn.

11. Claims 1-37 are rejected under 35 U.S.C. § 101 because the claimed invention allegedly lacks patentable utility. Applicants respectfully traverse this rejection.

The Office Action responds to Applicants' arguments by insisting that "no specific utility is asserted" by the present specification. Applicants maintain, however, that the present application – including the Abstract, the Overview on page 10, or the Summary of the Invention on page 4 – would convince a skilled artisan that Applicants had asserted the specific utility of treating or preventing ischemic damage in the application as filed. If the Examiner wishes to maintain this position, clarification is respectfully requested.

Based on this apparently unfounded assertion, the Office Action has adopted the further position that it is unnecessary to provide any documentary evidence that the rat models used in the Examples are not predictive of therapeutic effects to support the rejection based on lack of utility. Applicants are unaware of any legal basis that relieves the Examiner of this burden, and reiterate that this position is fundamentally at odds with the Federal Circuit decision in *Dickinson v. Zurko*, 119 S.Ct. 1816 (1999), which asserted that the PTO must establish a rational connection between the agency's fact-findings and its ultimate action. In light of Applicants' arguments of record, and the presumption in favor of Applicants, it is respectfully asserted that the present rejection is not supported by substantial evidence, and as such, fails to rise above the "arbitrary, capricious" standard applied under the "substantial evidence" test of Section 706(2)(E) of the Administrative Procedure Act. The Examiner has not cited any relevant art nor relied on any other fact-finding results to rebut the presumption in favor of Applicants. Applicants. If the Examiner is relying on evidence not of record, Applicants again request that such evidence be made of record to assist in rebuttal of this rejection. If the Examiner is relying on personal knowledge, Applicants respectfully request that the Examiner provide an affidavit pursuant to 37 C.F.R. 1.104(d)(2).

The Office Action further relies on Ex parte Balzarini, apparently to insist that human clinical trials would be required to support utility of the presently claimed subject matter.

Applicants respectfully point out, however, that unlike the claims in Balzarini the pending claims are not directed solely to the treatment of human stroke, but are more broadly directed to methods of limiting damage resulting from ischemia, methods of protecting cerebral tissue, and methods of treating stroke in *any* patient, human or otherwise, and no evidence has been made of record to support the bald assertion to the contrary on which this rejection is based.

In addition to the evidence already made of record to support the predictive role of the rat models used in the present application, Applicants submit herewith as Exhibit **A** excerpts from two searches of the PubMed database – one on "MCAO stroke" and the other on "rat focal stroke" – to show that prior to the filing of the present specification, the MCAO model specifically and focal stroke models generally had been used in dozens if not hundreds of experiments. Applicants further submit as Exhibit **B** abstracts of four papers supporting the acceptance and validity of focal ischemia models as predictive of ultimate therapeutic efficacy (Muir et al., *Stroke* **1998**, *29*, 918-923; Muir, *Magnes Res* **1998**, *11*, 43-56; Bullock et al., *Ann N Y Acad Sci* **1999**, *890*, 51-58; and Lees, *Cerebrovasc Dis* **2001**, *11*, 20-29). Accordingly, Applicants assert that the experiments performed in the Examples in the present application are sufficient to support the specific, asserted utility of the presently claimed methods. Reconsideration and withdrawal of this rejection are respectfully requested.

12. Claims 1 and 7 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection.

The Office Action maintains that the phrase "cerebral infarct volume" is unclear and inconsistent with the preamble recitation of neuronal cells. Applicants point again to the discussion above relating to the focal ischemia models discussed above, the results of which are frequently or even typically evaluated by measuring infarct size/volume (see even the titles of articles listed in Exhibit **A**). The specification need not define a term so commonly used in the art as to be generally recognized in the art. The Examiner has provided no documentary evidence to support any alleged inconsistent usage of this term in the art that would begin to suggest any lack of clarity of the meaning of this term to the skilled artisan. If the Examiner is relying on evidence not of record, Applicants again request that such evidence be made of record to assist in rebuttal

of this rejection. If the Examiner is relying on personal knowledge, Applicants respectfully request that the Examiner provide an affidavit pursuant to 37 C.F.R. 1.104(d)(2).

Regarding the assertion that the term "cerebral infarct volume" is inconsistent with the preamble recitation of neuronal cells, Applicants are unable to determine what this aspect of the rejection is intended to convey. The term "cerebral", referring as it does to neuronal tissue of the brain, points towards an underlying consistency, rather than inconsistency. Clarification is respectfully requested. Moreover, the asserted lack of clarity regarding the relationship between the "cerebral infarct volume" and the ptc therapeutic does not appear to be based on anything other than failure to recite specific dosages. Applicants contend, however, that the present claim language, like the term "'[e]ffective amount[,]' admirably states what is to be derived from the disclosure of the specification as to amount" (In re Caldwell, 138 U.S.P.Q. 243, 247) and is not unclear or indefinite. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim 7 is rejected as indefinite for being unclear as to the binding effect of the ptc therapeutic. Although Applicants believe this rejection is improper for reasons already made of record, Applicants have amended the pending claims to be directed to a commercially important embodiment. As amended, the claims do not recite this term, thereby rendering this rejection moot.

13-14. The specification is objected to on the basis that the term 'epoxic' should be corrected to 'hypoxic', as has already been done in the claims. Applicants have corrected the two locations in the specification where this term was used. Reconsideration and withdrawal of this rejection are respectfully requested.

15. Claims 1-37 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants have amended the pending claims to be directed to a commercially important embodiment, and have thus removed recitations of "therapeutic regimen" and "*ptc* therapeutic".

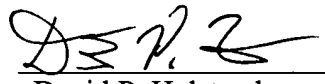
Applicants assume that this rejection does not extend to the term "*hedgehog* polypeptide" itself, as this term is used throughout the specification in relation to various embodiments of the invention. Nevertheless, Applicants point to support in the Summary of the Invention on page 4 as one specific location supporting the possession of the presently claimed invention as of the filing of the application. Reconsideration and withdrawal of this rejection are respectfully requested.

16-19. Claims 1-6, 13, and 34 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The terms and phrases objected to in the Office Action have been deleted from the claims as a result of the amendments discussed above, thereby rendering this rejection moot. Reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



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